REMARKS

Claims 1, 2 and 4-21 were rejected under 35 U.S.C. 112 on the grounds of failing to comply with the written description requirement. The rejection is predicated on an assertion that the application as originally filed lacks support for separate compositions containing alpha-ketoglutarate (α-KG) and/or alpha-ketoglutaric acid (α-KA) devoid of ammonium, and ammonium devoid of α-KG and α-KA. However, the application as originally filed clearly has support for such separate compositions. They are specifically described, for instance, on page 12 where the Group 1 animals received an infusion of ammonium chloride mixed only with saline, i.e. containing no α-KG or α-KA, whereas the Group 2 animals received α-KA without any ammonium.

The Board of Appeals in its remand questioned whether claim 1 required the administration of separate compositions. The independent claims in this case have been amended to make the separate administrations more explicit.

The Board of Appeals also focused on the open term "comprising" as possibly being sufficiently broadened so that the claims read on a α-KA/α-KG composition possibly containing ammonium and the ammonium composition possibly containing α-KA or α-KT. To ensure that the claims can not be so read, the independent claims have been amended to recite that any composition administered which contains at least one of the α-KA or α-KT is devoid of ammonium. As a result of this clarifying amendment, any possible interpretation of the claims is reading on a single composition has been eliminated and therefore the rejection of claims 1 and 6 under 35 U.S.C. 102 over Veech should be withdrawn.

The rejection of claims 1, 2 and 4-21 under 35 U.S.C. 103 over Veech and Vinnars in view Taconic and Bollish is respectfully traversed.

One of the predominant amino acids in the body, glutamine, is mainly utilized as an energy source and nitrogen carrier. Its availability is decreased during post-operative and posttraumatic catabolism, resulting in depletion of skeletal muscle glutamine and, with continued utilization of glutamine by the intestine, to low blood glutamine levels. While administration of glutamine to a patient in the state of glutamine depletion would appear to be desirable, it is less than a direct way of coping with the deficiency since glutamine is poorly soluble in water and cannot be sterilized by autoclavation. See, e.g., Vinnars at column 2. lines 30-40. A more direct way of preserving or raising blood glutamine levels is highly desirable.

The present invention provides a method of preserving body protein stored in a catabolic patient by the concomitant administration of a pair of pharmaceutical agents in amounts effective to preserve skeletal muscle. The first agent contains alpha-ketoglutarate (α-KG) and/or alpha-ketoglutaric acid (α-KA) and is devoid of ammonium. The second agent contains ammonium but is devoid of alpha-ketoglutarate and alpha-ketoglutaric acid.

Alpha-ketoglutarate (α-KG) is a biologic precursor of glutamine. Its use has been investigated in human internal and parental nutrition but in clinical studies, the recorded effects have been small and judged to be of minor importance. As noted infra, a recent study concludes there is no valid rationale for its use in an enteral composition.

Ammonium has been occasionally administered to patients in the form of a pharmacologically acceptable salt such as a chloride, despite the fact that it is considered a neurotoxin in that high concentrations are known to be neurotoxic. It causes metabolic acidosis. The recommended pharmaceutical uses of ammonium are few.

Nevertheless, the inventors found out that concomitant administration was advantageous. In another surprising finding, the inventors also found that infusion increased arterial glutamine concentration in a dose dependent fashion when the ammonium load was increased and the dose of α-KG was kept constant but not when the α-KG load was increased and the dose of ammonium was kept constant. Data establishing this surprising finding is presented in the application.

The primary reference relied on by the Examiner, Veech, relates to a parenteral nutritional aqueous solution which contains one or more of 20 metabolizable nitrogen containing compounds, one or more of 6 carboxylic metabolite anions and one or more of 5 cations. Among the 6 carboxylic metabolite anions is alpha-ketoglutarate and among the 5 cations is ammonium. The patent sets forth reasons for each of these materials to be present. It teaches that the presence of the metabolite anions in the composition of the Veech invention exert a desirable alkalinizing action which avoids metabolic acidosis. (col. 13, lines 62-65). The patent also points out that normal plasma contains concentrations of ammonium, α-KG and glutamate which is equivalent to the free mitochondrial free NAD/NADH ratio and if fluids are given which do not contain these substances, the cells alter their metabolism to realize that ratio. Accordingly, the presence of both α-KG and ammonium in the amino acid solution containing glutamate controls the redox state of the mitochondria. (col.13, line 66 to col. 14, line 20) Also, the presence of both ketoglutarate/glutamine at concentrations around the physiologically normal avoids the use of free ammonia, but generates ammonia and the production of intracellular glutamate. (col. 14, lines 21-24) Thus, the reference teaches the presence of both ammonium and α-KG in the same solution in order to control the redox state. Col. 13, line 66 et. seq. Further, the presence of both is designed to make the solution electrically neutral. (Col. 18, lines 51 et. seq.).

If the metabolite anion α-KG is present in the composition of the Veech for the purpose of avoiding metabolic acidosis, why would one employ a separate administration of a material such as ammonium which is known to cause metabolic acidosis when so administrated? There is no reason.

If the absence of ammonium or α-KG in a single fluid causes cells to alter their metabolism, why would one intentionally omit one? There is no reason.

If the presence of both α-KG and ammonium in the amino acid solution containing glutamate controls the redox state of the mitochondria, why would one be omitted? There is no reason.

If Veech teaches his combination avoids the use of free ammonia, why would one administer ammonium separately? There is no reason.

It will be appreciated from the foregoing, that the Veech reference teaches solution which contains a combination of alpha-ketoglutarate and ammonium in all instances and further provides reasons why both should be present. There is no reason or motivation to separate them.

Vinnars teaches the addition of alpha-ketoglutarate to a conventional amino acid solution but does not mention ammonium. Since this teaching is also found in Veech, the Vinnars reference does not add anything of substance vis-à-vis the instant rejection. Apparently, the only additional of disclosure in this reference on which reliance is being had is the fact that the concentration administered of the alpha-ketoglutarate should be at least 0.1g/kg body weight/day.

Vinnars points out that that glutamine reduction was not affected by enteral or parenteral nutritional support before the invention there described. He found that alpha-ketoglutarate worked in certain compositions even though ornithine-alpha-ketoglutarate had a limited effect and was not known whether there would be any clinical advantage (column 2, lines 11-20). A recent paper by Wiren (of record) describes a study to evaluate the feasibility of using α-ketoglutarate enrichment in enteral feeding and the effect on protein metabolism after major surgery. The authors concluded that enrichment of a whole protein-based formula with α-ketoglutarate did not improve protein metabolism or decrease muscle catabolism after major abdominal surgery. See e.g., the summary on page 725 and the concluding paragraph in the paper. The findings of the study were sufficiently important to elicit an editorial opinion (also of record). Note that the concluding sentence by Dr. Cynober in that opinion states that based on both the Wiren study and the available literature, there is no rationale for providing an α-ketoglutarate enriched enteral diet in post-operative patients. These teachings indicate that predictability in this art is limited.

The combination of references advanced in this rejection does not teach or suggest the use of two separate compositions, one containing alpha-ketoglutarate and/or alpha-ketoglutaric acid and the other containing ammonia, when neither of these compositions contain the other substance. The Veech reference discloses them but calls for a single solution containing both α-KG and ammonium, provides reasons both should be present and does not suggest separating them.

The Office Action seeks to overcome this basic deficiency by asserting that one skilled in the art would have been motivated to separate the two materials. The reason given is that both are known to be useful in methods of treating post-operative/post-

traumatic patients and normalizing/preserving skeletal muscle glutamine/nitrogen content. This attempted hindsight justification should be rejected for at least two reasons. First, there is no factual basis for the assertion that ammonium alone is known to be useful in such methods. The rejection does not identify where such disclosure is found nor has any such teaching been found in the references applied or elsewhere in the instant record. Veech does teach the use of ammonium but only within the same aqueous solution as the alpha-ketoglutarate and there is no implication it can be used separately. Quite the contrary, Veech provides a variety of reasons why the ammonium should be in the same composition as the α-KG and this is a second reason for rejecting the alleged motivation. If the presence of a material in a composition has been taught to provide advantages, then there must be a good reason existent before one skilled in the art would separate that material from the composition. The rejection does not even hypothesize such a reason.

In the case of *In re Freed*, 165 USPQ 570 (1970), the CCPA had occasion to observe that ". . . it seems more logical and reasonable to infer that one teaching a chemical reaction process would set out the least number of reactions thought to be necessary to accomplish the desired objectives." Applying similar logic, its seems more logical that one teaching a composition would want all of the components in a single composition so that the least number of compositions need be administered. Separating the components in the absence of a reason to do so is illogical.

The Office Action also attempts to provide motivation by asserting that "combining two agents which are known to be useful . . . into a single composition useful for the same purposes is prima facie obvious." But the invention does not involve combining two agents into a single composition. Two separate compositions

are used. Once again, it is respectfully submitted that one would not separate α-KG and ammonium in the absence of a reason and no reason has even been hypothesized.

The newly cited Taconic has apparently been cited to show the "normal" weight of certain male rats. That does not cure the basic deficiencies in the rejection.

The foregoing discussion has focused on claim 1. There are additional reasons why groups of the dependent claims are patentable over this art.

Claims 2-4 and 21 recited the duration of administration. Claim 20 (on which claim 21 is dependent) specifies that ammonium chloride is administered. There is no basis in the art to contend these claims are obvious.

Claim 6 specifies that the administrations are by infusion. Claim 7-10 and 15-19 specify rates of infusion. Beyond the fact that the references do not teach or suggest two separate infusions, there is no factual basis for selecting any rate of infusion. The Office Action attempts to overcome this deficiency by citing Bollish and asserting that the determination of amounts is mere optimization. Bollish merely shows that certain rates are within the realm of possibility. Accordingly, the assertion is merely a suggestion that it would be obvious to try various administration rates and find one which works, i.e., it is obvious to try various rates. It is well established that an obvious to try standard does not meet the requirements of §103.

Claims 11 - 14 recite that the infusion of the ammonium is increased over the period of administration. The art does not suggest changing the rate of administration of any material during the administration period for any reason. As noted earlier, changing the ammonium rate provides advantages which are not realized when the

rate of the α-KG is increased. Nothing in the art suggests the ammonium rate should be changed.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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